Remarks

The Specification

Substitute specifications were filed November 3, 2004 and February 10, 2005. A description of the amendments made to the specification was listed in the Request to File Substitute Specification filed February 10, 2005. However, in consideration of the Examiner's confusion and since these substitute specifications have not been entered, the amendments to the specification have been made as described above pursuant to 37 C.F.R. § 1.121. These amendments correspond to the substitute specification filed February 10, 2005.

The specification has been amended pursuant to 37 C.F.R. § 1.77 to include the appropriate section headers, "Background of the Invention," "Brief Summary of the Invention," "Detailed Description of the Invention," and "Brief Description of the Drawings."

Figure 1 has been converted to Tables A, B and C, since Figure 1 is not easily readable; and the specification has been amended to incorporate Tables A, B and C at page 28, line 23. Table A now correctly recites "NA nmol/l." NA as originally listed in Figure 1, now Tables A, B and C, is noradrenline. The specification has also been amended to delete all references to original Figure 1.

Original Figures 4 and 5 have been deleted and the remaining figures renumbered appropriately. The specification has also been amended to delete all refetences to original Figures 4 and 5. Please replace original Figures 2 and 3 with the replacement sheets submitted herewith as renumbered Figures 1 and 2, respectively. The specification has been amended to refer to newly renumbered Figures 1 and 2 as appropriate. Specifically, the specification has

been amended to refer to Figures 1 and 2, which were originally described in the specification on pages 20 and 21, under the section heading "Brief Description of the Drawings."

The specification has been amended to delete Examples 6-9 on pages 38-47. The specification has also been amended to renumber Examples 10-12 as Examples 6-8. The Examiner objected to the deletion of these Examples under 35 U.S.C. § 132(a) for **addition** of new matter. Contrary to the Examiner's assertion, the deletion of these examples does not contain new matter and does not change the scope of the application in any way. 35 U.S.C. § 132 (a) states that "no amendment shall **introduce** new matter into the disclosure of the invention." Furthermore the MPEP states that "35 U.S.C. 132 should be employed as a basis for objection to amendments to the abstract, specification, or drawings **attempting to add new** disclosure to that originally disclosed on filing." The Applicants have **not introduced or added** matter into the specification. They have deleted matter from the specification.

With respect to the Examiner's assertions that the omission of a feature can constitute new matter, omission of a feature or step in a method may broaden the disclosure and thus be considered new matter. However, this is clearly **not** the case in the present application. The Examiner cites MPEP Sections 706.03(o) and 1411.02 to support this assertion. MPEP Section 706.03(o) states "[n]ew matter includes not only the addition of wholly unsupported subject matter, but may also include adding specific percentages or compounds after a broader original disclosure, or even the omission of a step **from a method**." This is clearly not the case in the present application. MPEP Section 1411.02 is drawn to introduction of new matter in reissue applications. This is not a reissue application. Specifically, MPEP Section 1411.02 states that in

a reissue application "[n]ote that new matter may exist by virtue of the omission of a feature or of a step in a method. See United States Industrial Chemicals, Inc. v. Carbide & Carbon Chemicals Corp., 315 U.S. 668, 53 USPQ 6 (1942)." This clearly refers to instances where omission of a feature or step may broaden the disclosure and thus be considered new matter. "This court has uniformly held that the omission from a reissue patent of one of the steps or elements prescribed in the original, thus broadening the claims to cover a new and different combination, renders the reissue void, even though the result attained is the same as that brought about by following the process claimed in the original patent." *U. S. Industrial Chemicals, Inc. v. Carbide & Carbon Chemicals Corp.*, 315 U.S. 668, 678 (U.S. 1942). Again, this is clearly not the case in the present application. Therefore, the objection to the specification for deletion of subject matter is moot.

Objections to the Drawings

Replacement sheets are filed herewith for original Figures 2 and 3, renumbered as Figures 1 and 2, respectively. The Examiner objected to new Figure 1 (original Figure 2) because the Y axis is not labeled. The Y axis of Figure 1 now recites "NA nmol/l." The Examiner also objected to new Figure 2 (original Figure 3) because the Y axis was labeled as "cell mean" and not "aldosterone ng/ml." The Y axis of Figure 2 now recites "aldosterone ng/ml."

Rejection Under 35 U.S.C. § 112, first paragraph, enablement

Claims 1-4, 19 and 29-31 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner is correct in noting that the claims did not recite "cachexia." Applicants wish to note that cachexia is clearly defined as "weight loss due to underlying disease" in the specification at least at page 1, lines 3-5, lines 7-8 and page 4, lines 2-3. While applicants feel that "weight loss due to underlying disease" as previously recited in the claims would be clearly understood by one of ordinary skill in the art to mean cachexia, the claims have been amended to refer to a method of treating cachexia to avoid confusion.

The quantity of experimentation necessary for treating cachexia in a patient by administering an effective amount of an agent which reduces sympathetic nervous system activity is **not undue.** Applicants submit that a common mechanism (i.e. increased SNS activity) leads to cachexia in a number of patients with different diseases. Therefore, cachexia can be treated with drugs that are functionally-related by their ability to decrease SNS activity. See Tables A, B and C, previously Figure 1, in this respect.

One of ordinary skill in the art will be experienced in selecting and adjusting doses for a particular patient. Many known and approved drugs are available for use, ***now that the mechanism for treatment of cachexia is known.*** Therefore, one of ordinary skill in the art would also clearly be able to assess compatibility of the compound selected to treat cachexia with any other medications that the patient is taking based on information available to one of

skill in the art. It is not necessary for applicants to explain drug compatibility in the specification, as this is something that the skill person already assesses routinely on a patient-by-patient basis, based on standard reference sources, taking into account all the medications a patient is taking. The need to take into account all the medications a patient is taking is obvious and applies to any therapeutic regime. The test as affirmed by the Courts and the Board of Appeals has consistently been that one does not have to give every detail a health care provider would need, so long as sufficient detail was provided to enable the health care provider to practice the claimed method.

Applicants have demonstrated that **common features** are shared by cachexia patients arising from a wide range of different underlying conditions. On page 27, line 25 to page 28, line 9, the specification describes how cachexia relates to sympathetic nervous system activity and refers to Tables A, B and C and Figure 1 (original Figures 1 and 2), which demonstrate that patients with weight loss due to a number of diseases have elevated noradrenaline plasma levels (i.e. SNS activity) compared to controls. Accordingly, the Applicants have found that cachectic patients with a range of underlying diseases show a similar hormonal profile, and have described how to treat the weight loss with the agents listed on page 4, line 10 to page 13, line 22. Therefore, the compounds as defined by the claims and disclosed in the specification should be effective in treating cachexia regardless of the nature of the underlying disease.

Example 11, pages 53-55, discloses treatment of cachexia with carvedilol. Page 55, line 15 states that "beta-blocker treatment was beneficial in a cachectic patient." Example 12

discloses treatment of a cachexia patient with an aldosterone antagonist. Page 57, lines 14-15, discloses that aldosterone antagonist treatment was beneficial in a cachectic patient.

Applicants have further demonstrated a beneficial effect on cachexia following treatment with beta receptor blockers. The Examiner is directed to the enclosed abstract by Anker, et al. entitled "The impact of body mass index and body weight changes on prognosis in patients with chronic heart failure: results of the COMET study" which has been accepted for publication in Circulation at the end of October in the abstract supplement for the American Heart Association meeting taking place in November 2005.

A Declaration Under 37 C.F.R. § 1.132 submitted herewith provides additional examples that demonstrate enablement of the method as defined by the claims and described in the application as filed. The Declaration provides evidence of experiments conducted according to the guidance in the specification that demonstrate the beneficial effects on cachexia following treatment with beta receptor blockers, erythropoietin analogues and aldosterone antagonists. For example, the declaration describes that the inventors confidentially requested a colleague treat patients with cachexia due to cancer, a non-cardiovascular illness, with beta-blockers and spironolactone. The results from these experiments provided in the declaration demonstrate that cachexia was effectively treated with beta-blockers and spironolactone.

It is clear from the amount of direction and guidance presented in the specification, the state of the prior art, the relative skill of those in the art, that one of ordinary skill in the art could and did (as evidenced by the Declaration) use an agent which reduces sympathetic nervous

system activity to treat cachexia in a patient, as defined by the claims. Therefore, claims 1-4, 19 and 29-31 are enabled by the specification.

Rejection Under 35 U.S.C. § 112, first paragraph, written description

Claims 1-4 and 19 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The written description requirement for a claimed genus may be satisfied through a sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or a disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

The Examiner argues on page 9 of the office action that the claims fail to meet the written description requirement because "all possible" compounds that reduce SNS activity are not disclosed.

There is no legal requirement that applicants disclose all possible compounds that reduce SNS. Applicants have described the critical mechanism for treatment, the general class of compounds which are effective, and provided a number of representative species. Applicants

also demonstrated that a number of these representative species were effective in treating cachexia resulting from widely disparate diseases. ***This meets the legal requirements.***

Applicants have provided numerous species in the specification at least at page 4, line 10 to page 8, line 6 that reduce SNS activity. Furthermore, the representative number of species may be described by functional characteristic coupled with a **known** correlation between function and structure. The Applicants have discovered that a common mechanism (i.e. increased SNS activity) leads to cachexia in a number of patients with different diseases. Applicants have demonstrated as acknowledged by the Examiner on page 7 of the office action that patients with cachexia and increased SNS activity have elevated levels of aldosterone, noradrenaline and catecholamines (see pages 27, lines 12-15, page 28, lines 1-2, and page 29, lines 7-9, respectively). The Applicants have discovered that compounds falling within particular therapeutic classes, well known to one of ordinary skill in the art, are useful in treating cachexia by altering SNS activity through affecting the levels of these molecules. For example, the specification at least at example 11, pages 53-55, demonstrates that carvedilol, whose function (i.e. affects catecholamine levels) and structure are well known to one of ordinary skill in the art, is effective in treating a patient with cachexia. Additional compounds known to one of ordinary skill in the art that affect aldosterone, noradrenaline and catecholamine levels are described in the specification at least at page 4, line 10 to page 8, line 6. In addition, page 8, line to page 13, line 22, the specification further discloses publications in which many of the compounds are described in detail. As acknowledged by the Examiner it is not necessary to provide information well known to one of ordinary skill in the art.

The Applicants have clearly met the written description requirement by providing a description of a large number of species of compounds that have the functional characteristic required by the claims, whose structures are well known to one of ordinary skill in the art. Therefore, claims 1-4 and 19 satisfy the written description requirement.

Rejection Under 35 U.S.C. § 102

Claims 1-4, 19 and 29-31 were rejected under 35 U.S.C. § 102(b) as being anticipated by The RALES investigators, "Effectiveness of *Spironolactone* added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (The Randomized Aldactone Evaluation Study [RALES])" *The American Journal of Cardiology* 78:902-907 (1996). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As discussed above, claim 1 was amended to define a method of treating cachexia. The population treated with spironolactone in the RALES study is **not** the same population as specified in the claims as amended. RALES describes treating patients with chronic heart failure with spironolactone. RALES does not disclose or suggest selecting patients with cachexia, nor does it disclose that patients treated with spirolactone experienced weight gain.

In contrast to RALES, the method as defined by the claims relates to treatment of patients with cachexia. The claims do not define treatment of cachexia **candidates**. The claims as amended require selection of the patient on the basis of cachexia. As previously noted, not all patients with heart failure have cachexia (see page 27, lines 15-16; see also the enclosed copy of Hunt, et al., "ACC/AHA guidelines for the evaluation and management of chronic heart failure

in the adult: executive summary" *Journal of the American College of Cardiology* 38:7 (2102-2113 (2001) page 2109, first column).

Applicants describe in the specification at least at page 40, lines 3-5 in Example 4, that "patients with chronic heart failure who developed cardiac cachexia demonstrate particularly abnormal reflex control within the cardiovascular and respiratory systems." Therefore, cachexia is not merely a reflection of the underlying disease state, but is linked with particular parameters, not previously recognized.

As shown in the enclosed reference by Florea, et al., *Int. J. Cardiol.* 97:15-20 (2004) and Florea, et al., *American Heart J.* 144(1):45-50 (2002), there is no difference in cardiac function (as seen by either echocardiography or MRI) between patients with or without cachexia. For example the first paragraph of the Discussion of page 48 in Florea, et al., (2002), states that "the current study failed to detect any specific cardiac abnormalities in patients with cachectic CHF compared with patients with non-cachectic CHF when assessed in a cross-sectional study." Therefore, one of ordinary skill in the art would not consider that treatment of cardiac function would necessarily treat cachexia.

Additional treatments of heart failure (for example, diuretics, LV assist devices) with similar efficacy to, for example, beta receptor blockers, **do not** lead to weight gain, but instead weight loss, due to water loss. For example, see the enclosed reference by Clark, et al., *Eur. Heart J.* 22(24):2275-2283 (2001), which shows that another treatment for heart failure, use of a ventricular assist device, that improves patients' conditions, is not associated with weight gain.

It is also well known to one of ordinary skill in the art that diuretics (other than aldosteron antagonists) are an effective treatment for heart failure, and it is also well known that they do not improve cachexia and therefore are not useful for cachexia.

Weight loss is a sign of successful heart failure (HF) treatment when diuretics are used. The enclosed copy of Niebauer, et al., *Lancet* 353:1838-1842 (1999) illustrates the effect of diuretics. For example, page 1840, second paragraph of second column discloses that "intensive diuretic treatment for a mean 23 days (8) in ten patients with chronic heart failure resulted in a mean weight decrease of 3.6 kg (range 2.5-5.0), and improvement in the functional NYHA class in nine of ten patients." One of ordinary skill in the art would consider that diuretics produce weight loss when given to patients with heart failure. The use of diuretics as treatment in HF is indicated as per guidelines for HF therapy of the European Societyof Cardiology as well as the American Heart Association and American College of Cardiology (see for example page 2108 of the enclosed reference Hunt, et al., "ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary" *Journal of the American College of Cardiology* 38:7 (2102-2113 (2001); the European Society of Cardiology Guidelines, Remme and Swedberg, "Comprehensive guidelines for the diagnosis and treatment of chronic heart failure. Task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology" *European Journal of Heart Failure* 4:11-22 (2002) and Faris, et al., *Int. J. Cardiol.* 82:149-158 (2002). Therefore, treating and improving the underlying disease does not automatically lead to improvement in cachexia. The claims of the present application

disclose treatments for cachexia that are not dependent upon treatment of the symptoms of the underlying disease.

RALES does not disclose or suggest selecting patients with cachexia, nor does it disclose that patients treated with spirolactone exprienced weight gain. Therefore, claims 1-4, 19 and 29-31 are not anticipated by RALES.

Allowance of claims 1-27 and 29-31 is respectfully solicited.

Respectfully submitted,

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